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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,368	10/27/2000	Thomas N. Metcalf III	33377-00	6981

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EXAMINER	
GANGLE, BRIAN J	
ART UNIT	**PAPER NUMBER**
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/20/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/674,368	METCALF III ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) *3-6 and 9-42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 October 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-6-2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the response filed 1/8/2007 is acknowledged. The traversal is on the following ground(s).

Applicant argues:

1. That Rothbard does not meet the limitations of claim 1 and therefore does not anticipate the special technical feature of the claims. Applicant argues that Rothbard is directed to epitope mapping using synthetic peptides where rabbits were immunized with purified pili, and that these pili preparations are neither homogenous or recombinantly expressed, as is required by the claims. Applicant further argues that the claims require the composition to elicit a protective immune response in a human host, which Rothbard does not show.

2. That the European counterpart of this application was restricted into 4 groups, and that the 16 groups required by the examiner is excessive.

Applicant's arguments have been fully considered and deemed non-persuasive.

Regarding argument 1, as set forth previously, the purification or production of a product by a particular process does not impart novelty to that product. Rothbard discloses compositions comprising purified pilin proteins from *Neisseria gonorrheae*. The fact that these proteins were chemically synthesized rather than recombinantly produced does not render the claimed product novel. Further, regarding the homogenous nature of the product, Rothbard discloses a purification step, which is what is required by the claims. Regarding the requirement that the product serve as a vaccine that can elicit a protective immune response, this limitation is an intended use of the product and, as such, carries no patentable weight. Moreover, as the two products are the same, they would necessarily have the same immunological properties.

Regarding argument 2, the fact that the European counterpart was restricted serves as further evidence that lack of unity exists between the claimed inventions. Each case is examined based on its own merits and the actions of other agencies/examiners has no bearing whether a restriction requirement is proper.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-42 are pending. Claims 3-6 and 9-42 are withdrawn as being drawn to nonelected inventions. Claims 1-2 and 7-8 are currently under examination.

Specification

The use of the trademarks Tween, Stimulon, Triton, and others have been noted in this application in numerous places, including pages 23, 53, 55, and 70. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

It should be noted that the cited occurrences of improper use are only exemplary and applicant should review the specification to correct any other use of trademarks.

Information Disclosure Statement

The information disclosure statement filed 10/6/2005 has been considered. An initialed copy is enclosed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2 and 7-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a vast genus of immunogenic compositions comprising pilin proteins, specifically *Neisseria gonorrheae*. The claims encompass vaccines that contain any

pilin protein from the genus *Neisseria*, and more specifically *Neisseria gonorrheae*. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that applicant has possession the claimed invention. To adequately describe the genus of vaccine compositions comprising pilin proteins from the genus *Neisseria*, applicant must adequately describe the antigenic determinants (immunoepitopes) that elicit a protective immune response directed against any given pathogen, not just those determinants that would elicit an immune response to the polypeptide since given polypeptide can be immunogenic but not induce an immune response directed against any given disease.

The specification, however, does not disclose distinguishing and identifying features of a representative number of members of the genus of immunogenic compositions to which the claims are drawn, such as a correlation between the structure of the immunoepitope and its recited function (to elicit a protective immune response directed against *Neisseria*, and more specifically *Neisseria gonorrheae*), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus of immunogenic compositions.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is

severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104).

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. As evidenced by Greenspan *et al.* (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of immunoepitopes, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of immunogenic compositions capable of stimulating a protective immune response in a human to *Neisseria*, and more specifically *Neisseria gonorrheae* (as opposed to the polypeptide). Therefore, in accordance with the *Guidelines*, the description of immunoepitopes (antigenic determinants) is

not deemed representative of the genus of immunogenic compositions to which the claims refer. Hence, the claim does not meet the written description requirements.

Claims 1-2 and 7-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary.

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. Thus, Applicant assumes a certain burden in establishing that inventions involving physiological activity are enabled. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The instant claims are drawn to vaccine compositions (against an undisclosed disease) comprising pilin proteins from *Neisseria*, and more specifically *Neisseria gonorrheae*.

Breadth of the claims: The claims encompass all pilin proteins from *Neisseria*, and more specifically *Neisseria gonorrheae*, which provide protective immunity in humans against any given disease.

Guidance of the specification/The existence of working examples: The specification discloses pilin proteins from *Neisseria meningitidis* and *Neisseria gonorrheae* that are used in immunizations in mice and guinea pigs. The specification discloses various *in vitro* methods of determining the immune response raised in said animals. The specification is devoid of any teaching that the claimed composition provides an effective vaccine against any disease. To be a prophylactic composition, the composition must elicit protective immunity, demonstrable by pathogen challenge experiments in a reasonable model system. The skilled artisan would clearly realize the critical deficiency of this specification with respect to vaccines. There is absolutely no demonstration of protective immunity upon administration in any animal model of disease by the pilin proteins described in the specification. Therefore it is not clear that the described composition is capable of generating an active immune response that protects the animal against any type of disease.

State of the art: Although many investigators have tried to develop vaccines based on specific antigens, it is well understood that the ability of an antigen to stimulate antibody production does not necessarily correlate with the ability of the antigen to stimulate an immune response capable of protecting an animal from infection (Chandrashekar *et al.*, US Patent 6,248,329, col. 1, lines 35-41). It is well recognized in the vaccine art, that it is unclear whether an antigen derived from a pathogen will elicit protective immunity. Ellis (Chapter 29 of Vaccines, Plotkin, *et al.* (eds) WB Saunders, Philadelphia, 1998, especially p. 571, paragraph 2) exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies... and thus protect the host against attack by the pathogen." Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology. Consequently, the effects of sequence dissimilarities upon protein structure and function cannot be predicted. Bowie *et al* (Science, 1990, 247:1306-1310) teach that an amino acid sequence encodes a message that determines the shape and function of a protein and that it is the ability of these proteins to fold into unique three-dimensional structures that allows them to function, carry out the instructions of the genome **and form immunoepitopes**. Bowie *et al.* further teach that the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is

extremely complex. (column 1, page 1306). Bowie *et al* further teach that while it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of maintaining function are limited. Certain positions in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or no substitutions (column 2, page 1306). Additionally, as evidenced by Greenspan *et al.* (*Nature Biotechnology* 7: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan *et al.* recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan *et al.*, an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destabilizing to binding. Moreover, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows that the immunoepitopes that can elicit a protective immune response to a given pathogen can only be identified empirically. Furthermore, in the case of *Neisseria gonorrhoeae*, the gonococcal pilins display antigenic differences between strains as well as antigenic variation within a strain (Aho *et al.*, Infect. Immun., 65:2613-2620, 1997, IDS filed 10/6/2005, page 2613, paragraph bridging columns 1-2). Boslego *et al.* (Vaccine, 9:154-162, 1991, IDS filed 10/6/2005) disclosed a pilin vaccine that was successful in preventing gonococcal disease, but only when the challenge strain was identical to the vaccine seed strain (see page 154, column 2, paragraph 2). Boslego *et al.* also stated that there is no relevant animal model for the study of *Neisseria gonorrhoeae* infection, and that human challenge experiments do not always predict the efficacy of a vaccine against naturally occurring infections (page 154, column 2). The teachings of Aho *et al.* and Boslego *et al.* further suggest that one cannot predict the immune response that would be elicited by a composition comprised of neisserial pilin proteins.

The specification fails to teach that any of the claimed compositions can produce a protective response in the host, as is requisite of a vaccine composition. In view of the lack of support in the art and specification for an effective vaccine comprising the claimed proteins, it would require undue experimentation on the part of the skilled artisan to make and use the vaccine as claimed; therefore the claims are not enabled.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 contains the trademark/trade name Stimulon. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe an adjuvant and, accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Rothbard *et al.* (J. Exp. Med., 160:208-221, 1984).

The instant claims are drawn to vaccine compositions comprising an isolated and purified recombinantly-expressed pilin protein of the genus *Neisseria*, wherein said vaccine composition elicits a protective immune response in a human host (claim 1); wherein the pilin protein is from the species *Neisseria gonorrhoeae* (claim 2).

Rothbard *et al.* disclose an immunogenic composition containing *Neisseria gonorrhoeae* pili (see paragraph bridging pages 209-210). The products of the prior art reference appear to be the same as the product claimed by the applicant because they appear to possess the same or similar functional characteristics, i.e. an immunogenic composition and a vaccine comprising *Neisseria gonorrhoeae* pilin proteins. The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPO 964 (CAFC 1985); In re Marosi, 218 USPO 289, 29222-293 (CAFC 1983); In re Brown, 173 USPO 685 (CCPA 1972). The term "vaccine" is an intended use and is given no patentable weight, therefore the claims are drawn to a composition comprising *Neisseria gonorrhoeae* pilin proteins. Therefore, Rothbard *et al.* meet the limitations of claims 1-2.

Claims 1-2 and 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Buchanan *et al.* Bacterial Vaccines, Chapter 21, IDS filed 10/6/2005).

The instant claims are drawn to vaccine compositions comprising an isolated and purified recombinantly-expressed pilin protein of the genus *Neisseria*, wherein said vaccine composition elicits a protective immune response in a human host (claim 1); wherein the pilin protein is from the species *Neisseria gonorrhoeae* (claim 2); further comprising an adjuvant, diluent, or carrier (claim 7); wherein the adjuvant is selected from the group consisting of aluminum hydroxide, aluminum phosphate, Stimulon, QS-21, 3-O-deacylated monophosphoryl lipid A, IL-12, and wild-type or mutant cholera toxin (claim 8).

Buchanan *et al.* disclose gonococcal pili vaccines (page 160, column 1). A vaccine comprising purified gonococcal pilin proteins and aluminum phosphate as an adjuvant was disclosed (see page 160, column 2 and page 161, column 1). The products of the prior art reference appear to be the same as the product claimed by the applicant because they appear to possess the same or similar functional characteristics, i.e. an immunogenic composition and a vaccine comprising *Neisseria gonorrhoeae* pilin proteins. The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product

are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPO 964 (CAFC 1985); In re Marosi, 218 USPO 289, 29222-293 (CAFC 1983); In re Brown, 173 USPO 685 (CCPA 1972). Therefore, Buchanan *et al.* meet the limitations of the claims.

Claims 1-2 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Boslego *et al.* (Vaccine, 9:154-162, 1991, IDS filed 10/6/2005).

The instant claims are drawn to vaccine compositions comprising an isolated and purified recombinantly-expressed pilin protein of the genus *Neisseria*, wherein said vaccine composition elicits a protective immune response in a human host (claim 1); wherein the pilin protein is from the species *Neisseria gonorrhoeae* (claim 2); further comprising an adjuvant, diluent, or carrier (claim 7).

Boslego *et al.* disclose a vaccine composition comprising purified *Neisseria gonorrhoeae* pilus protein and saline. The products of the prior art reference appear to be the same as the product claimed by the applicant because they appear to possess the same or similar functional characteristics, i.e. an immunogenic composition and a vaccine comprising *Neisseria gonorrhoeae* pilin proteins. The purification or production of a product by a particular process does not impart novelty or unobviousness to a product when the same product is taught by the prior art. This is particularly true when properties of the product are not changed by the process in an unexpected manner. See In re Thorpe, 227 USPO 964 (CAFC 1985); In re Marosi, 218 USPO 289, 29222-293 (CAFC 1983); In re Brown, 173 USPO 685 (CCPA 1972). Therefore, Boslego *et al.* meet the limitations of the claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian J. Gangle whose telephone number is (571) 272-1181. The examiner can normally be reached on M-F 7-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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